AUSTRALIAN PRODUCT INFORMATION

ZEMPREON CFC-FREE INHALER

(salbutamol (as sulfate))

1 NAME OF THE MEDICINE

Salbutamol sulfate B.P.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ZEMPREON Inhaler is a pressurised metered dose inhaler which delivers 100 micrograms of salbutamol (as sulfate) per actuation.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Pressurised inhalation

ZEMPREON Inhaler (with dose counter): Suspension contained in an aluminium alloy can, sealed with a metering valve. The canister has a counter attached to it and is fitted with a plastic actuator incorporating an atomising nozzle and fitted with a mouthpiece cover.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ZEMPREON Inhaler is indicated for the relief of bronchospasm in patients with asthma or chronic obstructive pulmonary disease, and for acute prophylaxis against exercise-induced asthma and other stimuli known to induce bronchospasm.

4.2 DOSE AND METHOD OF ADMINISTRATION

ZEMPREON Inhaler is administered by the inhaled route only, to be breathed in through the mouth.

Increasing use of beta-2 agonists may be a sign of worsening asthma. Under these conditions a reassessment of the patient's therapy plan may be required and concomitant glucocorticosteroid therapy should be considered.

As there may be adverse effects associated with excessive dosing, the dosage or frequency of administration should only be increased on medical advice.

Adults and children

If required, one or two inhalations, repeated four-hourly. The bronchodilator effect of each administration of ZEMPREON Inhaler lasts for at least four hours and more frequent use should be unnecessary. The patient can readily recognise any reduction in the length of action and should be instructed to consult a doctor if the effect of a previously adequate dose lasts for less than three hours.

For detailed instructions on how to use ZEMPREON Inhaler refer to the patient information leaflet.

Note 1: Failure to obtain relief from the inhaler may be a medical emergency. Other appropriate treatment must be instituted without delay.

Note 2: It is important that the patient be instructed in the proper use of the pressurised aerosol.

Note 3: Instruct the patient to wash the plastic actuator with warm water and let it air-dry completely at least once a week, to prevent build-up of medicine in the plastic actuator and ensure proper dosing.

Geriatric

Initial doses of salbutamol in the elderly should be lower than the recommended adult dosage. The dose may then be gradually increased if sufficient bronchodilatation is not achieved.

In impaired liver function

As about 60% of orally administered salbutamol (this includes not only tablet and syrup preparations but also approximately 90% of an inhaled dose) is metabolised to an inactive form, impairment of liver function may result in accumulation of unchanged salbutamol.

In impaired renal function

About 60-70% of salbutamol administered by inhalation or intravenous injection is excreted in urine unchanged. Impairment of renal function may therefore require a reduction in dosage to prevent exaggerated or prolonged effects.

4.3 CONTRAINDICATIONS

Hypersensitivity to any of the ingredients.

Non-i.v. formulations of salbutamol must not be used to arrest uncomplicated premature labour or threatened abortion.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The management of asthma should normally follow a stepwise program, and patient response should be monitored clinically and by lung function tests. Increasing use of short-acting inhaled beta-2 agonists to control symptoms indicates deterioration of asthma control. Despite multiple contributory factors, overuse of short acting beta-agonists (multiple SABAs, more frequent use of SABAs, monotherapy with high dose SABAs) during management of acute severe asthma exacerbations may mask the progression of underlying disease and cause deterioration of asthma control leading to poor clinical outcomes (increased severity and mortality). Under these conditions, the patient's therapy plan should be reassessed. Sudden and progressive deterioration in asthma control is potentially life-threatening and consideration should be given to starting or increasing corticosteroid therapy. In patients considered at risk, daily peak flow monitoring may be instituted.

Patients should be warned that if either the usual relief is diminished or the usual duration of action reduced, they should seek medical advice at the earliest opportunity after increasing the dose.

Animal studies suggest that cardionecrotic effects may occur with high dosages of some sympathomimetic amines. On this evidence the possibility of the occurrence of myocardial lesions cannot be excluded subsequent to long term treatment with these drugs.

Care should be taken with patients who are known to have received large doses of salbutamol or other sympathomimetic drugs, or who are suffering from hypertension, hyperthyroidism, myocardial insufficiency, or diabetes mellitus.

ZEMPREON Inhaler contains a hydrofluoroalkane (norflurane) propellant. In animal studies, norflurane has been shown to have no significant pharmacological effects, except at very high exposure concentrations when narcosis and a relatively weak sensitisation to the arrhythmogenic effects of catecholamines were found. The potency of the cardiac sensitisation was less than that of trichloromethane (CFC-11).

Salbutamol should be administered cautiously to patients with thyrotoxicosis.

Excessive use may induce a non-responsive state leading to a worsening of hypoxaemia.

Potentially serious hypokalaemia may result from beta-2 agonist therapy mainly from parenteral and nebulised administration. Particular caution is advised in acute severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids, diuretics and hypoxia. It is recommended that serum potassium levels are monitored in such situations.

The possibility of cardiac arrhythmias arising as a consequence of salbutamol induced hypokalaemia should be borne in mind, especially in digitalised patients, following the administration of salbutamol injection.

As with other inhalation therapy, paradoxical bronchospasm may occur, resulting in an immediate increase in wheezing after dosing. This should be treated immediately with an alternative presentation or a different fast-acting inhaled bronchodilator, if immediately available. The specific salbutamol presentation should be discontinued, and if necessary a different fast-acting bronchodilator instituted for ongoing use.

Spacer Devices

Most patients, particularly those with poor inhaler technique, will benefit from the consistent use of a spacer device with their metered dose inhaler (MDI or "puffer"). Use of a spacer will also decrease the amount of drug deposited in the mouth and back of the throat, and therefore reduce the incidence of local side effects such as "thrush" and a hoarse voice.

In those people using a spacer, a change in formulation of the drug used, or a change in the make of spacer, may be associated with alterations in the amount of drug delivered to the lungs. The clinical significance of these alterations is uncertain. However, in these situations, patients should be monitored for any loss of asthma control.

If using a spacer, the patient should be instructed to actuate the inhaler into the spacer and then slowly breathe in as far as possible. The patient should hold their breath for as long as comfortable, before breathing out slowly. This should be repeated for each actuation of the drug into the spacer. Any delays between actuation and inhalation should be kept to a minimum.

Static on the walls of the spacer may cause variability in drug delivery. Patients should be advised to wash the spacer in warm water and detergent and allow it to air dry without rinsing or drying with a cloth. This should be performed before initial use of the spacer and at least monthly thereafter.

Use in the Elderly

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Geriatric for dosage requirements.

Paediatric Use

There are no special precautions for use in children.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Beta-adrenergic blocking drugs inhibit the bronchodilator action of salbutamol and other sympathomimetic bronchodilators. However, such drugs should not be used in asthmatic patients as they may increase airway resistance. Salbutamol and non-selective beta-blocking drugs, such as propranolol, should not usually be prescribed together.

Care is recommended if it is proposed to administer salbutamol in concomitant therapy with other sympathomimetic amines as excess sympathetic stimulation may occur.

Animal studies have shown that large doses of salbutamol may interact with imipramine, chlordiazepoxide and chlorpromazine but any practical significance of these results in man remains to be established.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

There is no information on the effects of salbutamol on human fertility. Reproductive studies in rats revealed no evidence of impaired fertility.

Use in Pregnancy

Pregnancy Category: A

Salbutamol is known to cross the placental barrier in humans. Safety for use in pregnancy has not been demonstrated, therefore the drug should not be used in pregnant women, or those likely to become pregnant, unless the expected benefit outweighs any potential risk.

Oral administration of salbutamol to rats and rabbits during pregnancy showed no teratogenic effects in offspring, but evidence of retardation of fetal development was recorded in an inhalational teratology study in rabbits at an estimated dose of 149 µg/kg/day.

During worldwide marketing experience, rare cases of various congenital anomalies, including cleft palate and limb defects have been reported in the offspring of patients being treated with salbutamol.

Although intravenous salbutamol and occasionally salbutamol tablets are used in the management of uncomplicated premature labour, ZEMPREON presentations should not be used for threatened abortion during the first or second trimesters of pregnancy. Intravenous salbutamol is contra-indicated in cases of ante-partum haemorrhage because of the risk of further haemorrhage from an atonic uterus and there is the risk of the same problem arising inadvertently in asthmatics using salbutamol. Profuse uterine bleeding following spontaneous abortion has been reported after the use of salbutamol. Special care is required in pregnant diabetic women.

Use in Lactation

As salbutamol is probably secreted in breast milk, its use in nursing mothers is not recommended unless the expected benefit to the mother is greater than any possible risk to the infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

A fine tremor of skeletal muscle has been reported in some patients when salbutamol is administered orally or by inhalation, the hands being the most obviously affected, with a few patients feeling tense. These effects are dose related and are caused by a direct action on skeletal muscle and not by direct CNS stimulation.

With higher doses than those recommended, or in patients who are unusually sensitive to beta-adrenergic stimulants, dilatation of some peripheral arterioles may occur leading to a small reduction in arterial pressure; a compensatory increase in cardiac output may then occur. Tachycardia may occur in some patients.

Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles) have been reported. Peripheral vasodilation and a compensatory small increase in heart rate may occur in some patients.

Other reactions which may occur are headaches, nausea, palpitations and sensations of warmth. Hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension and collapse have been reported very rarely. There have been very rare reports of muscle cramps and thrombocytopenia. Mouth and throat irritation may occur with inhaled salbutamol.

Note: The incidence and severity of particular side effects depends on the dosage and route of administration. ZEMPREON does not cause difficulty in micturition because, unlike sympathomimetic drugs such as ephedrine, therapeutic doses have no alpha-adrenergic receptor stimulant activity.

Potentially serious hypokalaemia may result from beta-2 agonist therapy.

As with other inhalation therapy the potential for paradoxical bronchospasm should be kept in mind, resulting in an immediate increase in wheezing after dosing (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

As with other beta-2 agonists, hyperactivity has been reported rarely in children.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The most common signs and symptoms of overdose with salbutamol are transient beta-agonist pharmacologically mediated events (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). The signs of salbutamol overdosage are significant tachycardia and/or significant muscle tremor.

Hypokalaemia may occur following overdosage with salbutamol. Serum potassium levels should be monitored.

Lactic acidosis has been reported in association with high therapeutic doses as well as overdoses of short-acting beta-agonist therapy, therefore monitoring for elevated serum lactate and consequent metabolic acidosis (particularly if there is persistence or worsening of tachypnea despite resolution of other signs of bronchospasm such as wheezing) may be indicated in the setting of overdose.

Consideration should be given to discontinuation of treatment and appropriate symptomatic treatment such as a cardio-selective beta-blocking agent given by intravenous injection, in patients presenting with cardiac symptoms (e.g. tachycardia, palpitations). Beta-blocking drugs should be used with caution as they may cause bronchospasm in sensitive individuals.

In treating overdosage with ZEMPREON Inhaler, it is to be remembered that forty 100 microgram puffs of the inhaler contain as much salbutamol as one 4 mg salbutamol tablet.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Salbutamol is a relatively selective beta-2 adrenoreceptor stimulant. It is more specific than both isoprenaline and orciprenaline for adrenergic beta-2 receptors.

Pharmacodynamics

After oral and parenteral administration, stimulation of the beta receptors in the body, both beta-1 and beta-2, occurs because (a) beta-2 selectivity is not absolute, and (b) higher concentrations of salbutamol occur in the regions of these receptors with these modes of administration. This results in the beta-1 effect of cardiac

stimulation, though not so much as with isoprenaline, and beta-2 effects of peripheral vasodilatation and hypotension, skeletal muscle tremor and uterine muscle relaxation.

Metabolic effects such as hyperinsulinaemia and hyperglycaemia also may occur, although it is not known whether these effects are mediated by beta-1 or beta-2 receptors. The serum potassium levels have a tendency to fall.

Clinical Trials

Salbutamol, delivered from a pressurised metered-dose inhaler using chlorofluorocarbon (CFC) propellants, has been used for over 20 years in clinical practice and has been demonstrated to be safe and effective in the treatment of reversible obstructive airways disease. The following section describes clinical studies conducted to assess the therapeutic equivalence of salbutamol reformulated using a non-chlorofluorocarbon propellant, with the established product.

A clinical program was devised that included paediatric and adult patients, smokers and patients aged over 65 years. A total of 1064 patients were randomised and received study medication in six clinical studies. Of these, 586 received the CFC-free inhaler (approx. 81 patient-years) and 572 received CFC containing product (approx. 79 patient-years). All studies compared the CFC-free product against CFC product.

Three single dose crossover studies, two bronchial provocation studies with histamine and a dose-ranging bronchodilatation study, in adults demonstrated the efficacy of salbutamol formulated with the non-chlorofluorocarbon propellant. Another bronchial provocation study demonstrated efficacy in paediatric patients.

Two randomised, double-blind, parallel group multiple dosing studies were also conducted in adults. In a four-week '100 µg prn' dosing study (n=423), patients with mild to moderate reversible airways obstruction demonstrated equivalent usage of inhaled salbutamol (daily median usage of 4 actuations/day) in both treatment groups. In a twelve-week 200 µg qds dosing study (n=547), patients with moderate reversible airways obstruction recorded no change in heart rate (as a measure of tolerability) following the treatment period, and no detrimental effect was seen as a result of 'switching' from the CFC containing inhaler to the CFC-free inhaler.

These studies in both adult and paediatric patients showed that the CFC-free inhaler at the same dose is clinically equivalent to, and is as well tolerated as the CFC containing inhaler. There was no evidence to suggest any possible interactions between salbutamol and non-chlorofluorocarbon propellant. There were no reports of hypokalaemia or paradoxical bronchospasm in the clinical programme. No new or unexpected adverse events were highlighted when compared to the CFC containing inhaler.

5.2 PHARMACOKINETIC PROPERTIES

Following inhalation, salbutamol acts topically on bronchial smooth muscle and initially the drug is undetectable in the blood. After 2 to 3 hours low concentrations are seen, due presumably to the portion of the dose which is swallowed and absorbed in the gut.

The elimination half-life of inhaled or oral salbutamol is between 2.7 and 5 hours.

Salbutamol is not metabolised in the lung but is converted to the 4'-o-sulfate ester in the liver. Salbutamol is excreted in the urine as free drug and as the metabolite. After oral administration 58-78% of the dose is excreted in the urine in 24 hours, approximately 60% as metabolites. A small fraction is excreted in the faeces.

Impairment of liver or renal function may necessitate a reduction in dosage (see Section 4.2 DOSE AND METHOD ADMINISTRATION).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity and Carcinogenicity

Salbutamol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium in a 2-year study in the rat at oral doses of 2, 10 and 50 mg/kg. In another study this effect was blocked by the coadministration of propranolol. These findings are a drug class effect and are thought not to be relevant to the clinical use of the drug. An 18-month study in mice and a lifetime study in hamsters revealed no evidence of tumorigenicity. Studies with salbutamol revealed no evidence of mutagenesis.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Non-chlorofluorocarbon propellant 1,1,1,2-tetrafluoroethane (GR106642X or HFA-134a or norflurane).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Replace the mouthpiece cover firmly and snap it into position.

Store below 30ºC. Protect from frost and direct sunlight. As with most inhaled medications in pressurised canisters, the therapeutic effect of this medication may decrease when the canister is cold.

Pressurised container. Do not expose to temperatures higher than 50°C.

6.5 NATURE AND CONTENTS OF CONTAINER

ZEMPREON Inhaler comprises of a suspension of salbutamol sulfate in the propellant HFA-134a.

Container type: The suspension is contained in an aluminium alloy can, sealed with a metering valve. Each canister is fitted with a plastic actuator incorporating an atomising nozzle and fitted with a mouthpiece cover.

Pack sizes: Each canister contains at least 200 actuations.

ZEMPREON Inhaler is available with or without a counter (see Section 3 PHARMACEUTICAL FORM). The counter shows how many actuations of medicine are left. The number is visible through a window in the back of the plastic actuator.

Some container types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 335999 – ZEMPREON CFC-FREE INHALER Salbutamol 100 microgram (as sulfate) pressurised inhaler metered dose (with counter)

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

The canister should not be punctured, broken or burnt even when apparently empty.

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

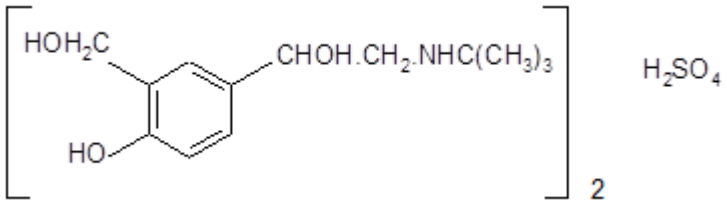
Chemical Name

di[(RS)-2-(1,1-dimethylethyl)amino-1-(4-hydroxy-3-hydroxymethylphenyl)ethanol]sulfate.

Molecular Formula

$C_{26}H_{44}N_2O_{10}S$

Chemical Structure



CAS Number

51022-70-9

Description

Salbutamol sulfate is a white or almost white crystalline powder, freely soluble in water, practically insoluble or very slightly soluble in ethanol (96 per cent) and in methylene chloride.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S3 (Pharmacist Only Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

7/05/2020

10 DATE OF REVISION

30/08/2024

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial change
4.4	Additional information in relation to overuse of short acting beta-agonists.

4.8	Addition of very rare adverse event reports of thrombocytopenia.

ZEMPREON_WITH COUNTER_pi\Aug24/00 (CCDS 29-Jan-2024)